09/384,379

FILE 'BIOSIS, MEDLINE, CAPLUS, WPIDS' ENTERED AT 14:18:34 ON 30 JAN 2003

L1	115	S MEDULLASIN
L2	23927	S SERINE PROTEASE
L3	46	S L1 AND L2
L4	22	DUP REM L3 (24 DUPLICATES REMOVED)
L5	2	S L4 AND MONOCLONAL ANTIBODY
L6	9	S L1 AND MONOCLONAL ANTIBODY
L7	5	DUP REM L6 (4 DUPLICATES REMOVED)

2001 0016331 A1

1/30/03

L7 ANSWER 1 OF 5 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-608141 [70] WPIDS
DNN N2001-454062 DNC C2001-180861
TI Immunological measurement of human **medullasin** useful in diagnosing multiple sclerosis involves the use of anti-human **medullasin** antibody.
DC A89 B04 D16 S03
IN AOKI, Y; KATSURAGI, H; SUZUKI, H; TAKAHASHI, K
PA (DAIC) DAINICHISEIKA COLOR & CHEM MFG CO LTD
CYC 30
PI EP 1122543 A1 20010808 (200170)* EN 20p
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
AU 2000072180 A 20010809 (200170)
CA 2327414 A1 20010803 (200170) EN
JP 2001221801 A 20010817 (200170) 8p
NO 2001000175 A 20010806 (200170)
CN 1307237 A 20010808 (200173)
JP 2001289859 A 20011019 (200201) 8p
JP 2001305141 A 20011031 (200204) 7p
ADT EP 1122543 A1 EP 2000-123141 20001025; AU 2000072180 A AU 2000-72180 20001212; CA 2327414 A1 CA 2000-2327414 20001201; JP 2001221801 A JP 2000-26828 20000203; NO 2001000175 A NO 2001-175 20010111; CN 1307237 A CN 2000-134432 20001130; JP 2001289859 A JP 2000-293004 20000926; JP 2001305141 A JP 2000-121587 20000421
PRAI JP 2000-121587 20000421; JP 2000-26828 20000203; JP 2000-26829 20000203
AB EP 1122543 A UPAB: 20011129
NOVELTY - Measurement of human **medullasin** (I) content in blood involves breaking up leukocytes in the blood sample by contacting with aqueous liquids ((i) (osmotic pressure of not more than 250 or not less than 310 mOsm/kg.H2O) and (ii) (liquid comprising a hemolysate)) and immunologically determining the amount of (I) released into the blood sample from the leukocytes using an anti-human **medullasin** antibody.
USE - In diagnosing multiple sclerosis by observing the size and/or changes in (I).
ADVANTAGE - (I) In blood can be accurately measured with good reproducibility. The method provides a simple diagnosis method by which diagnosis of the disease, understanding of the state of the disease and assumption of consequence can be carried out. The value of (I), do not differ between male and female and also according to age.
Dwg.0/5

L7 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2000:343515 BIOSIS
DN PREV200000343515
TI A novel endoproteolytic processing activity in mitochondria of erythroid cells and the role in heme synthesis.
AU Dzikaite, Vijole; Kanopka, Arvydas; Brock, Jeremy H.; Kazlauskas, Arunas;

Melefors, Ojar (1)
CS (1) Microbiology and Tumor Biology Center, Karolinska Institutet, SE-171 77, Stockholm Sweden
SO Blood, (July 15, 2000) Vol. 96, No. 2, pp. 740-746. print.
ISSN: 0006-4971.
DT Article
LA English
SL English
AB The erythroid isoform of aminolevulinate synthase (eALAS) protein is a major control point in erythroid heme synthesis and hemoglobin formation. Erythroid cells were extracted from mouse blood and bone marrow and metabolically labeled with 35S-methionine. This was followed by immunoprecipitation of eALAS protein products. The results show that the N-terminus of the expected full-length 59-kd form of the eALAS protein is truncated in bone marrow erythroid cells by approximately 7 kd. More differentiated erythroid cells in the peripheral blood exhibit very little of this protein truncation. Erythroid cells from the bone marrow were isolated using **monoclonal antibody** TER-119 and were shown to contain a unique endoprotease activity that could cleave the eALAS protein to the shorter form in vitro. With or without the mitochondrial signal sequence, the eALAS protein could serve as a substrate for the cleavage. This cleavage renders a functional eALAS protein and only removes a domain of unclear function, which has previously been reported to vary in size as a result of alternative RNA splicing. The protease activity was enriched from the membranes of mitochondria from bone marrow cells and was shown to be different from mitochondrial processing peptidase, **medullasin**, and other known proteases. Apart from the mitochondrial processing peptidase that cleaves the import signal sequence, this is the first description of a mitochondrially located site-specific processing protease activity.

L7 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2000:482865 BIOSIS
DN PREV200000482865
TI Determination of **medullasin** levels for the diagnosis of multiple sclerosis.
AU Aoki, Y. (1); Saida, T.; Nakano, I.; Saito, T.; Ikeguchi, K.; Urabe, T.; Nishiguchi, E.; Suzuki, H.; Takahashi, K.; Katsuragi, H.; Mizuno, Y.
CS (1) Department of Food and Health Sciences, Faculty of Human Life Sciences, Jisssen Women's University, Osakaue 4-1-1, Hino-City, Tokyo, 191-8510 Japan
SO Acta Neurologica Scandinavica, (October, 2000) Vol. 102, No. 4, pp. 218-221. print.
ISSN: 0001-6314.
DT Article
LA English
SL English
AB Objectives: To obtain a simple and reliable clinical parameter for the diagnosis of multiple sclerosis among patients with neurological diseases.
Patients and methods: Heparinized peripheral blood was obtained from

patients with multiple sclerosis and those with non-inflammatory neurological diseases and healthy volunteers. A new enzyme immunoassay method determining **medullasin** levels in human granulocytes was developed by using mouse **monoclonal antibody** against **medullasin**. Results: A newly developed enzyme immunoassay method for **medullasin** can detect as little as 1 ng/ml **medullasin** and results can be obtained within 2 h. Eighty-five out of 112 patients with multiple sclerosis (75.8%) showed positive results (above means of normals+2 SD) in the **medullasin** test, while 15.4% (12/78) of patients with non-inflammatory neurological disease had positive results. Conclusion: This newly developed enzyme immunoassay method for **medullasin** is considered to be a useful paraclinical test for the diagnosis of multiple sclerosis.

L7 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1999:361718 CAPLUS
DN 131:43586
TI Preparation of anti-human **medullasin monoclonal antibody** for immunoassay
IN Aoki, Yosuke; Suzuki, Hideaki; Takahashi, Shigeyoshi; Katsuragi, Hisashi
PA Dainichi Seika Kogyo K. K., Japan
SO Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 11151085	A2	19990608	JP 1997-336303	19971120
PRAI JP 1997-336303		19971120		

AB Provided is an IgG-type mouse **monoclonal antibody** to human **medullasin**, a serine protease in granulocytes. **Medullasin** prepd. from human granulocytes was used to immunize BALB/c mice and the immunized spleen cells were fused with mouse P3-X63-Ag8-U1 (P3U1) myeloma cells to prep. hybridoma cells secreting the **monoclonal antibody**. Use of the **monoclonal antibody** for immunoassay of **medullasin** during clin. diagnosis of chronic inflammatory diseases or multiple sclerosis was shown.

L7 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1992:282375 BIOSIS
DN BA94:7025
TI INDUCTION OF ACTIVATED KILLER CELLS FROM HUMAN LYMPHOCYTES BY **MEDULLASIN** A SERINE PROTEASE IN BONE MARROW CELLS.
AU AOKI Y; HASE T; OSHIMI K; SUZUKI K
CS DEP. BIOCHEM. NUTR., INST. PUBLIC HEALTH, MANATO-KU, TOKYO, JPN.
SO IMMUNOLOGY, (1992) 75 (3), 481-487.
CODEN: IMMUAM. ISSN: 0019-2805.
FS BA; OLD
LA English
AB **Medullasin**, a serine protease found in human bone marrow cells, has been shown to induce activated killer (AK) cells that lyse both

natural killer (NK)-sensitive and -resistant cloned target cells from human lymphocytes. In addition to all the tested malignant cell lines, malignant cells obtained from all patients with acute myelocytic leukaemia, chronic lymphocytic leukaemia and lymphoblastic leukaemia were lysed by AK cells induced by **medullasin**. Maximum induction was achieved when lymphocytes were incubated at 37% for 60 min in the presence of **medullasin** (20 .mu.g/ml). The cytotoxicity of AK cells induced by **medullasin** treatment (200 .mu.g/ml, 37% for 60 min) was greater than that of lymphokine-activated killer (LAK) cells produced by 500 U/ml of interleukin-2 (IL-2). Cytokines such as IL-2 or interferon (IFN) are not considered to be involved in the **medullasin** induction of AK cells for the following reasons: (1) neither IL-2 nor IFN activity were detected in the supernatant of lymphocytes treated with **medullasin**; (2) the supernatant of lymphocytes treated with **medullasin** failed to induce AK cells; and (3) the presence of antibodies against IL-2 or IFN did not influence the effect of the protease. By employing monoclonal antibodies to the surface antigen of lymphocytes and a panning method using plastic dishes coated with anti-mouse IgG goat Fab', progenitor as well as effector cells were found to be CD16-positive cells.

=>

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 12 3141

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	BIOLOGICAL ABSTRACTS, vol. 78, Philadelphia, PA, US; abstract no. 37324, XP002169075 * abstract * & Y. AOHI ET AL.: "MEDULLASIN ACTIVITY IN GRANULOCYTES OF PATIENTS WITH MULTIPLE SCLEROSIS ." ANNALES OF NEUROLOGY, vol. 15, no. 3, 1984, pages 245-249, New York, NY USA ---	1-18	G01N33/573 G01N33/68
X	CHEMICAL ABSTRACTS, vol. 134, Columbus, Ohio, US; abstract no. 204585, XP002169076 * abstract * & Y. AOKI ET AL.: "Enzyme immunoassay of medullasin in peripheral blood " CLINICA CHEMICA ACTA, vol. 178, no. 2, New York NY USA ---	1-18	
X,P	MEDLINE, Washington DC USA; abstract no. 20520784, *abstract* XP002169074 & Y. AOKI ET AL.: " Determination of medullasin levels for the diagnosis of multiple sclerosis " ACTA NEUROLOGICA SCANDINAVICA, vol. 102, no. 4, 1 October 2000 (2000-10-01), pages 218-221, Copenhagen DK -----	1-18	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)
G01N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	7 June 2001	Van Bohemen, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

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		Publication Date	6/8/99
		Language	Japanese
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1/5/1 (Item 1 from file: 351)

012582368
WPI Acc No: 1999-388475/199933
Anti-human medullasin monoclonal anti-body for sclerosis patients - useful for diagnosing human medullasin in blood
Patent Assignee: DAINICHISEIKA COLOR & CHEM MFG CO LTD (DAIC)
Inventor: AOKI Y; KATSURAGI H; SUZUKI H; TAKAHASHI K
Number of Countries: 002 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 11151085	A	19990608	JP 97336303	A	19971120	199933	B
CA 2281262	A1	20010228	CA 2281262	A	19990831	200120	N

Priority Applications (No Type Date): JP 97336303 A 19971120; CA 2281262 A 19990831
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 11151085	A		7	C12N-005/10	
CA 2281262	A1	E		C12P-021/08	

Abstract (Basic): JP 11151085 A

NOVELTY - Anti-human medullasin monoclonal anti-body identifies the human medullasin existing in granulocytes. DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the anti-body manufacturing method. Antibody forming cell and myeloma cell extracted from an animal which is immune to human medullasin is fused to form hybridoma which is cultured. Antibody is then extracted from the culture.

USE - The labeled antibody is fixed in an insoluble carrier. The sample containing human medullasin is contacted with the carrier, when the human medullasin is caught on the carrier. The labeled complex is then assayed (claimed). For inflammatory diseases like multiple sclerosis.

ADVANTAGE - The immunological assay of human medullasin is carried out quickly and easily.

Dwg.0/2

Derwent Class: B04; D16; S03
International Patent Class (Main): C12N-005/10; C12P-021/08
International Patent Class (Additional): C07K-016/40; C12N-005/12; C12N-015/02; G01N-033/53; G01N-033/543; G01N-033/573; G01N-033/577; C12P-021/08; C12R-001-91

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FILE 'BIOSIS, MEDLINE, CAPLUS, WPIDS' ENTERED AT 14:18:34 ON 30 JAN 2003

L1	115	S MEDULLASIN
L2	23927	S SERINE PROTEASE
L3	46	S L1 AND L2
L4	22	DUP REM L3 (24 DUPLICATES REMOVED)
L5	2	S L4 AND MONOCLONAL ANTIBODY
L6	9	S L1 AND MONOCLONAL ANTIBODY
L7	5	DUP REM L6 (4 DUPLICATES REMOVED)
L8	236	S L2 (P) LEUKOCYTES
L9	114	DUP REM L8 (122 DUPLICATES REMOVED)
L10	9	S L9 AND GRANULOCYTE#

date

8/27/99

6/8/99